DOCKET NO: 264821US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
STEFAN LAUFER, ET AL.	: EXAMINER: MORRIS, P. L.
SERIAL NO: 10/524,486	:
FILED: NOVEMBER 17, 2005	: GROUP ART UNIT: 1625
FOR: 2-THIO-SUBSTITUTED IMIDAZOLE DERIVATIVES AND THEIR USE IN PHARMACEUTICS	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal of the Final Rejection dated December 11, 2007 of Claims 16-37. A Notice of Appeal is **submitted herewith**.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Merckle GmbH, Chemische-pharmazeutische Fabrik, having an address at Graf-Arco-Strasse 3, 89079 Ulm, Germany.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and the assignee are aware of no appeals, interferences, or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 16-37 stand rejected and are herein appealed. Claims 1-15 have been canceled.

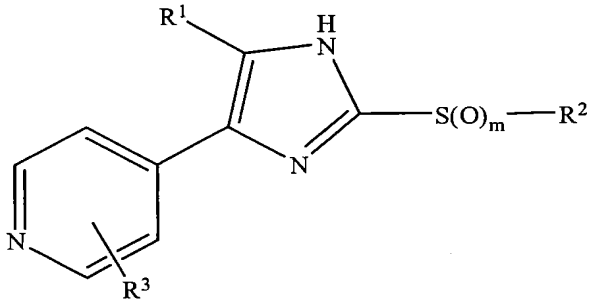
IV. STATUS OF THE AMENDMENTS

An amendment under 37 CFR 1.116 has been filed on February 26, 2008. The CLAIMS APPENDIX attached herewith assumes entry of the amendment, since it simply corrects minor errors.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

A summary of the claimed subject matter, as claimed in independent Claim 16 and 25, is mapped out below, with reference to page and line numbers in the specification added in **[bold]** after each element.

The subject matter of Claim 16 is a 2-thio-substituted imidazole derivative compound of the formula I **[page 2, lines 27-28]**



[page 3, lines 1-2]

wherein

R^1 is aryl which may or may not be substituted by a halogen atom; **[page 3, lines 4-5]**

R^2 is selected from the group consisting of **[page 3, line 7]**

a) aryl-C_1-C_4-alkyl, **[page 3, line 9]** and

b) C_1-C_6-alkyl; **[page 3, line 15]**

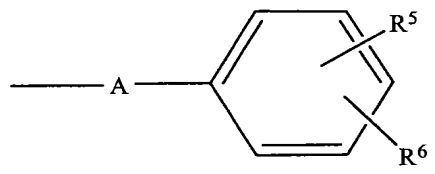
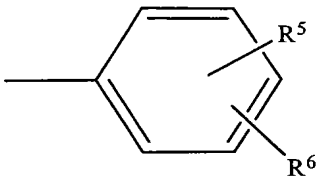
R^3 is selected from the group consisting of **[page 3, line 18]**

a) NR^4R^{10} **[page 3, line 20]**

b) NR^7COR^{10}, **[page 3, line 21]** and

c) C_1-C_6-alkoxy; **[page 101, line 28]**

R^4 is H; **[page 4, line 24]**

R^{10} is  or 

or, if R^3 is NR^7COR^{10}, is R^8, **[page 102, lines 3-6]**

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy or C_1-C_6-alkyl; **[page 4, lines 26-27 or page 102, lines 7-8]**

R^7 is H, C_1-C_6-alkyl or benzyl; **[page 4, line 30 or page 102, line 10]**

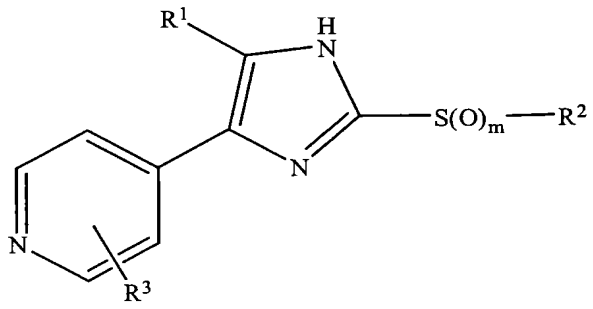
R^8 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl or phenyl, where the phenyl group may have one or two substituents independently of one another selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and halogen; **[page 102, lines 12-14]**

A is straight-chain or branched C_1-C_6-alkylene or C_2-C_6-alkenylene **[page 5, line 4 or page 102, line 16]** and

m is 0, 1 or 2; **[page 6, line 16 or page 102, line 19]**

or a tautomer, an optical isomer or a physiologically acceptable salt thereof. **[page 6, line 20]**

The subject matter of Claim 25 is a 2-thio-substituted imidazole derivative compound of the formula I **[page 2, lines 27-28]**



wherein

R^1 is aryl which is substituted by a halogen atom or by halo-C_1-C_6-alkyl; **[page 3, lines 4-5]**

R^2 is selected from the group consisting of **[page 3, line 7]**

a) aryl-C_1-C_4-alkyl, **[page 3, line 9]** and

b) C_1-C_6-alkyl; **[page 3, line 15]**

R^3 is selected from the group consisting of **[page 3, line 18]**

a) NR^4R^{10}, **[page 3, line 20]**

b) NR^7COR^{10}, **[page 3, line 21]**

c) OR^{10}, **[page 4, line 6]** and

d) NH_2; **[page 4, line 16]**

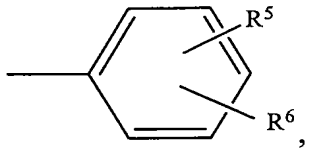
R^4 is H, $-COR^{14}$, $-CO_2R^{14}$, $-CONH_2$, $-CONHR^{14}$, $-CHR^{16}-OR^{14}$, $-CHR^{16}-O-COR^{14}$, $-COC(R^{16})_2-OH$, $-COR^{15}$, SO_2R^{15} or $-SO_2R^{14}$, R^{14} is C_1-C_6-alkyl or CF_3, R^{15} is phenyl or tolyl, and R^{16} is H or C_1-C_6-alkyl; **[page 4, line 24 and page 8, lines 10-14]**

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy, C_1-C_6-alkyl or halo-C_1-C_6-alkyl; **[page 4, lines 26-27 or page 102, lines 7-8]**

R^7 is H; **[page 4, line 30 or page 102, line 10]**

R^{10} has one of the meanings below: **[page 4, line 31]**

a) A — B, **[page 4, line 32]**

b) 

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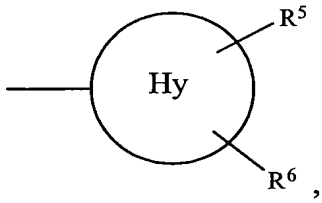
c) 

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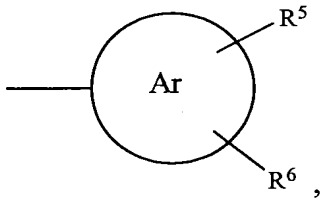
d) 

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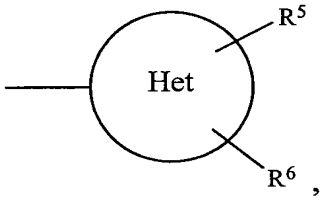
e) 

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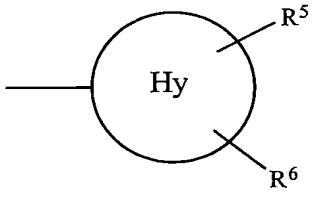
f) C_1-C_6-alkyl which is substituted by 2 phenyl groups, or

g) trifluoromethyl; **[page 5, lines 1-3]**

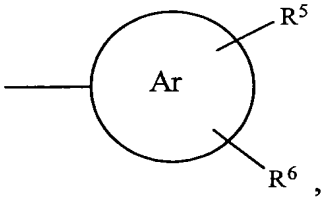
A is straight-chain or branched C_1-C_6-alkylene or C_2-C_6-alkenylene;

B is selected from the group consisting of **[page 5, line 6]**

a) H,

b) 

, **[page 5, last line]**

c) 

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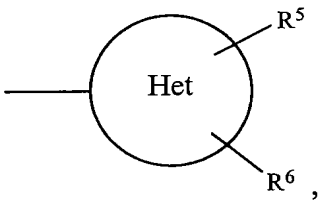
d) 

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e) OC_1-C_6-alkyl, **[page 6, first three lines]** and

f) OH; **[page 6, fifth line]**

Hy is a 3- to 10-membered non-aromatic mono-, bi- or tricyclic carbocycle which may or may not be fused with a benzene ring; **[page 6, lines 4-5]**

Ar is a 5- or 6-membered aromatic heterocycle which has 1, 2 or 3 heteroatoms independently of one another selected from the group consisting of O, S and N and which may or may not be fused with a benzene ring; **[page 6, lines 7-9]**

Het is a 5- or 6-membered non-aromatic heterocycle which has 1, 2 or 3 heteroatoms independently of one another selected from the group consisting of O, S and N which may or may not be fused with a benzene ring and which may or may not be bridged bicyclically or tricyclically; **[page 6, lines 11-14]**

m is 0, 1 or 2; **[page 6, line 16]**

or a tautomer, an optical isomer or a physiologically acceptable salt thereof. **[page 6, line 20]**

VI. GROUNDS OF REJECTION

Ground (A)

Claims 16-37 stand rejected under 35 U.S.C. § 103(a) as unpatentable over "the combined teachings of" US 6,432,988 (Laufer et al). [1]

[1] In a telephone conversation with undersigned counsel on February 19, 2008, the Examiner confirmed that the rejection is over Laufer et al alone.

Ground (B)

Claims 16-34 stand rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-8, 10, 13 and 14 of Laufer et al.

Ground (C)

Claims 16-34 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-17 of copending Application No. 10/514,911 (copending application).

Ground (D)

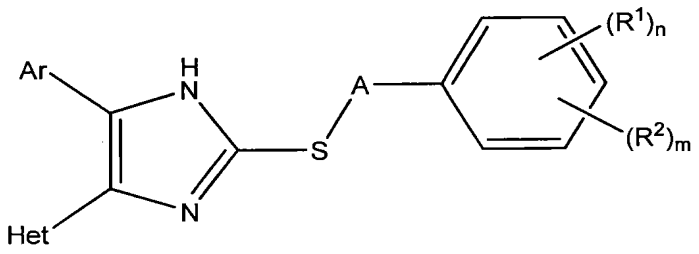
Claims 24, 34, 36 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

VII. ARGUMENT

Ground (A)

Claims 16-37 stand rejected under 35 U.S.C. § 103(a) as unpatentable over US 6,432,988 (Laufer et al). That rejection is untenable and should not be sustained.

Laufer et al discloses 4-heteroaryl-5-phenylimidazole derivatives having 2-arylalkylthio, 2-arylalkenylthio, or 2-arylalkynylthio substitution, and having the following general formula I:



(I)

wherein, *inter alia*, A is a straight-chain or branched, saturated or unsaturated alkylene chain having up to six carbon atoms (column 2, lines 42-43); R^1 is C_{1-4}-alkylthio, C_{1-4}-alkylsulfinyl, C_{1-4}-alkylsulfonyl, sulfonamide or C_{1-4}-alkylcarbonyl (column 2, lines 44-45); and n is 1 or 2 (column 2, line 49). Thus, R^1 is necessarily present. In other words, the compounds of Laufer et al have a substituted phenylalkyl group attached to a sulfur atom. The present claims, on the other hand, although R^2 may be aryl-C_1-C_4-alkyl, do not embrace the compounds of Laufer et al, since the specification makes clear that when aryl is intended to be permissibly substituted, the applicable substituents are specifically described. See, for example, page 3, lines 9-13. In other words, in the present claims, "aryl" means "unsubstituted aryl."

No motivation is provided to modify Laufer et al's compounds, such as by expanding its genus to include n as 0 (zero), which is the same as modifying Laufer et al's R^1 group to be, in effect, hydrogen.

In addition, the Declaration under 37 C.F.R. § 1.132 of named co-inventor Dr. Wolfgang Albrecht (Albrecht Declaration) shows that representative compounds according to the present invention exhibit surprisingly higher activity compared to representative compounds of Laufer et al. The table in the Declaration contains pharmacological data obtained by means of a test method described therein. The higher the values given in the table, the more active are the compounds as inhibitors of p38 MAP kinase, which is indicative of an anti-inflammatory effect.

In the Final Rejection, the Examiner finds that Laufer et al "generically embrace the instant compounds."

In reply, as discussed above, Laufer et al does **not** *embrace* the present compounds; rather, Laufer et al's compounds and the presently-claimed compounds are mutually

exclusive. In addition, there is no motivation to modify Laufer et al's compounds since, as discussed above, n is required to be 1 or 2 only.

In the Final Rejection, the Examiner finds that the Albrecht Declaration is "of little if any prohibitive value because it is not commensurate in scope with the claims and fails to include the closest prior art compounds, *i.e.*, wherein R^{10} represents -A-phenyl (optionally substituted) and the **elected** compound of example 54" (emphasis by the Examiner).

In reply, aside from the fact that there is no *prima facie* case of obviousness and therefore, no showing of unexpected results is required, nevertheless, the Albrecht Declaration includes the closest prior art compounds and the elected species compound of Example 54 of the present invention (which is compound no. 18 therein.) In Example 54, R^3 is NR^4R^{10}, wherein R^{10} is tetrahydropyran-4-yl. Note also that the second comparative compound of Laufer et al in the Albrecht Declaration (last compound listed in the table) is the second compound recited in Claim 8 of Laufer et al.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

Ground (B)

Claims 16-34 stand rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-8, 10, 13 and 14 of Laufer et al. That rejection is untenable and should not be sustained.

The claims of Laufer et al are no more pertinent than the complete disclosure, discussed above under Ground (A). There is no overlap between the present claims and those of Laufer et al, nor is there any suggestion to modify the compounds claimed in Laufer et al.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

Ground (C)

Claims 16-34 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-17 of copending Application No. 10/514,911 (copending application). That rejection is untenable and should not be sustained.

The Examiner is respectfully requested to hold the rejection in abeyance until the present claims are found to be allowable but for this rejection or the copending application has been patented. See M.P.E.P. 822.01.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

Ground (D)

Claims 24, 34, 36 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. That rejection is untenable and should not be sustained.

It is respectfully submitted that the data described in the specification at page 29 herein in Table 1 are based on well-established *in vitro* tests for predicting activity against inflammatory disorders in which TNF-α and IL-β are involved, such as rheumatoid arthritis. While the Examiner purports to list the so-called *Wands* factors, nevertheless, the Examiner has not convincingly indicated why the results in said Table, or the description generally in the specification, would not enable a person skilled in the art to treat inflammatory disorders of the type recited in the claims.

While inflammatory disorders such as rheumatoid arthritis are described as treated by the present invention by immunomodulating and/or cytokine-releasing-inhibiting action, and the Examiner finds that current treatments of rheumatoid arthritis are inadequate and that the

art recognizes that specific anti-rheumatic drugs do not inhibit all cytokines and the mechanisms of action are unclear, nevertheless, it is the Examiner's burden to show that the presently-disclosed *in vitro* data would not be accepted by persons skilled in the art as indicative of *in vivo* behavior. The Examiner, in effect, requires *in vivo* data, which is not required by current case precedent.

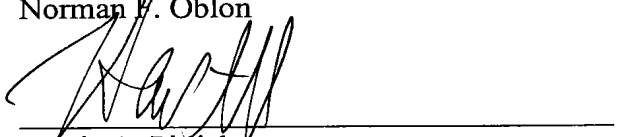
For all the above reasons, it is respectfully requested that this rejection be REVERSED.

VIII. CONCLUSION

For the above reasons, it is respectfully requested that all the rejections still pending in the Final Rejection be REVERSED.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Harris A. Pitlick
Registration No. 38,779

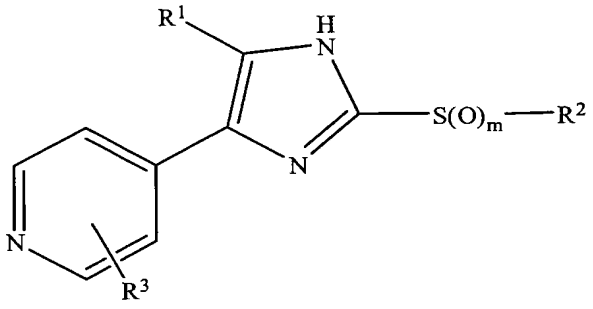
Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 03/06)

NFO:HAP\

CLAIMS APPENDIX

Claim 16: A 2-thio-substituted imidazole derivative compound of the formula I



wherein

R^1 is aryl which may or may not be substituted by a halogen atom;

R^2 is selected from the group consisting of

a) aryl-C_1-C_4-alkyl, and

b) C_1-C_6-alkyl;

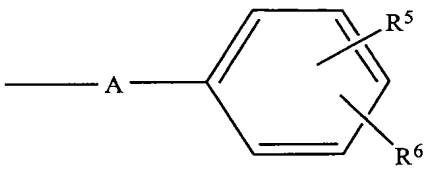
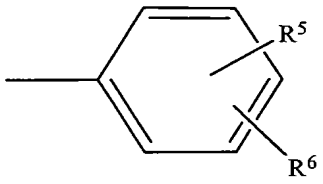
R^3 is selected from the group consisting of

a) NR^4R^{10}

b) NR^7COR^8, and

c) C_1-C_6-alkoxy;

R^4 is H;

R^{10} is  or 

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy or C_1-C_6-alkyl;

R^7 is H, C_1-C_6-alkyl or benzyl;

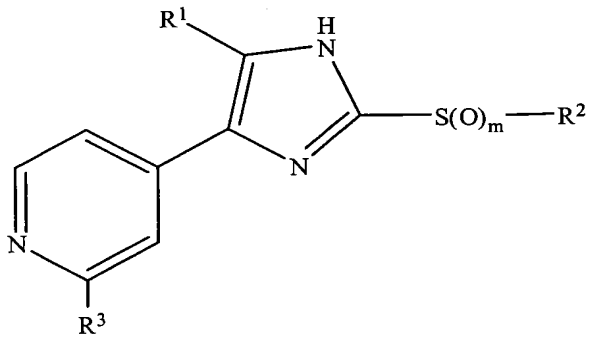
R^8 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl or phenyl, where the phenyl group may have one or two substituents independently of one another selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and halogen;

A is straight-chain or branched C_1-C_6-alkylene or C_2-C_6-alkenylene and

m is 0, 1 or 2;

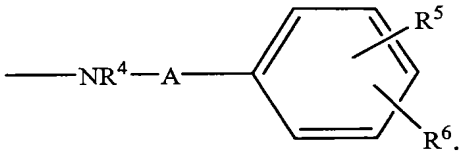
or a tautomer, an optical isomer or a physiologically acceptable salt thereof.

Claim 17: The compound as claimed in claim 16, which has the formula Ia:



Ia

Claim 18: The compound as claimed in claim 16, wherein R^3 is



Claim 19: The compound as claimed in claim 18, wherein A is C_1-C_2-alkylene.

Claim 20: The compound as claimed in claim 18, wherein A is ethylidene.

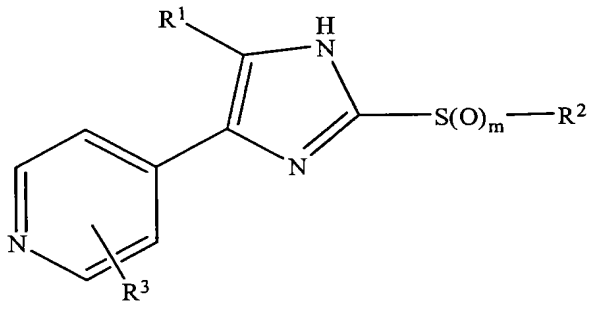
Claim 21: The compound as claimed in claim 18, wherein R^5 and R^6 are H.

Claim 22: The compound as claimed in claim 16, wherein R^1 is 4-fluorophenyl.

Claim 23: A pharmaceutical composition, comprising at least one compound as claimed in claim 16, and one or more pharmaceutically acceptable carriers and/or additives.

Claim 24: A method for treating inflammatory disorders in which TNF-α and IL-β are involved which comprises administering to a person in need of such a treatment an amount of a compound as claimed in claim 16 sufficient to have anti-inflammatory action.

Claim 25: A 2-thio-substituted imidazole derivative compound of the formula I



wherein

R^1 is aryl which is substituted by a halogen atom or by halo-C_1-C_6-alkyl;

R^2 is selected from the group consisting of

a) aryl-C_1-C_4-alkyl, and

b) C_1-C_6-alkyl;

R^3 is selected from the group consisting of

a) NR^4R^{10},

b) NR^7COR^{10},

c) OR^{10}, and

d) NH_2;

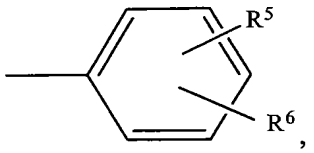
R^4 is H, $-COR^{14}$, $-CO_2R^{14}$, $-CONH_2$, $-CONHR^{14}$, $-CHR^{16}-OR^{14}$, $-CHR^{16}-O-COR^{14}$, $-COC(R^{16})_2-OH$, $-COR^{15}$, SO_2R^{15} or $-SO_2R^{14}$, R^{14} is C_1-C_6-alkyl or CF_3, R^{15} is phenyl or tolyl, and R^{16} is H or C_1-C_6-alkyl;

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy, C_1-C_6-alkyl or halo-C_1-C_6-alkyl;

R^7 is H;

R^{10} has one of the meanings below:

a) A — B,

b) 

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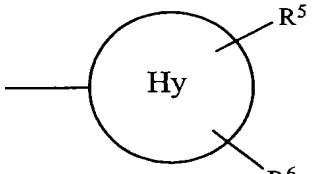
c) 

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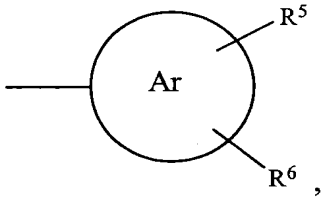
d) 

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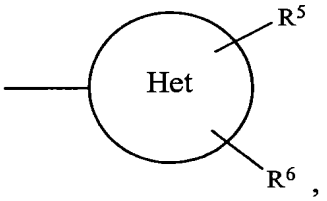
e) 

,

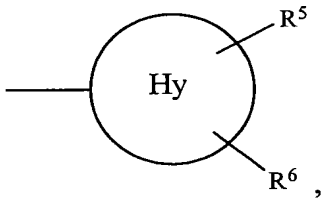
f) C_1-C_6-alkyl which is substituted by 2 phenyl groups, or

g) trifluoromethyl;

A is straight-chain or branched C_1-C_6-alkylene or C_2-C_6-alkenylene;

B is selected from the group consisting of

a) H,

b) 

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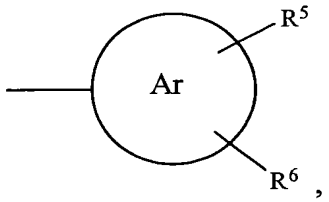
c) 

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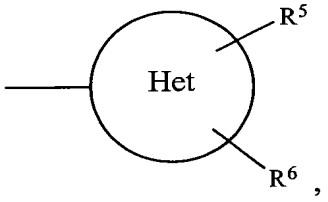
d) 

,

e) OC_1-C_6-alkyl, and

f) OH;

Hy is a 3- to 10-membered non-aromatic mono-, bi- or tricyclic carbocycle which may or may not be fused with a benzene ring;

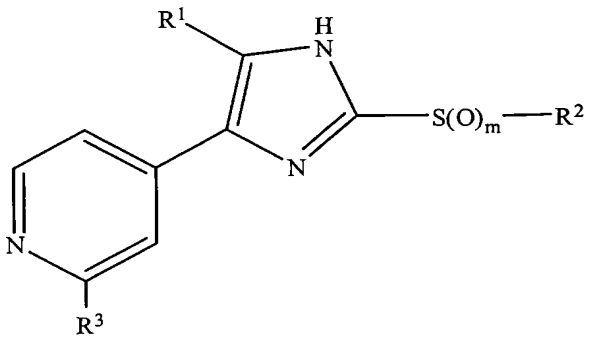
Ar is a 5- or 6-membered aromatic heterocycle which has 1, 2 or 3 heteroatoms independently of one another selected from the group consisting of O, S and N and which may or may not be fused with a benzene ring;

Het is a 5- or 6-membered non-aromatic heterocycle which has 1, 2 or 3 heteroatoms independently of one another selected from the group consisting of O, S and N which may or may not be fused with a benzene ring and which may or may not be bridged bicyclically or tricyclically;

m is 0, 1 or 2;

or a tautomer, an optical isomer or a physiologically acceptable salt thereof.

Claim 26: The compound as claimed in claim 25, which has formula Ia:



Ia

Claim 27: The compound as claimed in claim 25, wherein R^{10} is A-B and B is selected from the group consisting of OC_1-C_6-alkyl and OH.

Claim 28: The compound as claimed in claim 25, wherein R^3 is NR^7COR^{10}, and R^{10} is selected from the group consisting of -O-C_1-C_4-alkylphenyl, phenyl and C_2-C_6-alkenyl which is substituted by phenyl.

Claim 29: The compound as claimed in claim 25, wherein A is C_1-C_2-alkylene.

Claim 30: The compound as claimed in claim 25, wherein A is ethylidene.

Claim 31: The compound as claimed in claim 25, wherein R^5 and R^6 are H.

Claim 32: The compound as claimed in claim 25, wherein R^1 is halogen-substituted phenyl or CF_3-substituted phenyl.

Claim 33: A pharmaceutical composition, comprising at least one compound as claimed in claim 25, and one or more pharmaceutically acceptable carriers and/or additives.

Claim 34: A method for treating inflammatory disorders in which TNF-α and IL-β are involved which comprises administering to a person in need of such a treatment an amount of a compound as claimed in claim 25 sufficient to have anti-inflammatory action.

Claim 35: The compound as claimed in claim 25, which is {4-[5-(4-fluorophenyl)-2-methylsulfanyl-1H-imidazol-4-yl]-pyridin-2-yl}-(tetrahydropyran-4-yl)amine.

Claim 36: The method according to claim 24, wherein the inflammatory disorder is rheumatoid arthritis.

Claim 37: The method according to claim 34, wherein the inflammatory disorder is rheumatoid arthritis.

EVIDENCE APPENDIX

Declaration under 37 C.F.R. § 1.132 of named co-inventor Dr. Wolfgang Albrecht (Albrecht Declaration), filed October 24, 2007.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	: Stefan Laufer *et al.*
SERIAL NO.	: 10/524,486
FILED	: November 17, 2005
FOR	: 2-Thio-substituted imidazole derivatives and their use in pharmaceutics

DECLARATION UNDER 37 C.F.R. §1.132

COMMISSIONER OF PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

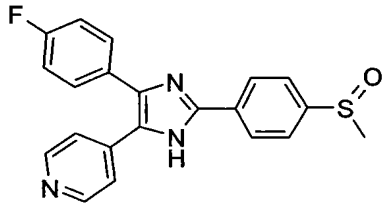
SIR:

Now comes Dr. Wolfgang Albrecht, co-inventor of the above identified invention, who deposes and states:

1. I am a graduate of Biotechnology, and received my doctorate degree from the Technical University in Berlin in the year 1990.
2. I have been working for Merckle since 1993. Since 2001, I have been leading the drug discovery programs at Merckle.
3. I have read and fully understood U.S. application, Ser. No. 11/321,631.
4. I have read and fully understood the Office Action of May 30, 2007 and the prior art cited therein.
5. The following experiments and investigations were carried out by me or under my direct supervision.

A number of compounds of the above identified application were prepared by the methods disclosed in said application and then subjected to the following test:

Microtiter plates were coated with the p38 MAP kinase substrate ATF-2 by incubating 50 µl of 20 µg/ml ATF-2 for one hour at 37°C. After the plates were washed three times with water, 50 µl of kinase mixture (= 50 mM Tris-HCl, 10 mM $MgCl_2$, 10 mM β-glycerol phosphate, 10 µg/ml BSA, 1 mM DTT, 100 µM ATP, 100 µM Na_2VO_4, 10 ng activated p38α) without an with increasing inhibitor concentrations were added into the wells and incubated for one hour at 37°C. The plates were washed three times with water and incubated with an anti-phospho-ATF-2 antibody for one hour at 37°. Thereafter, the plates were again washed three times with water and incubated with a goat, alkaline phosphatase-labeled anti-rabbit IgG, for one hour at 37°C. The plates were washed and incubated with 100 µl of a solution containing the phosphatase substrate 4-nitrophenolphosphate (3 mM 4-NPP, 50 mM $NaHCO_3$, 50 mM $MgCl_2$) for 1.5 hours at 37°C. Formation of 4-nitrophenolate was measured at 405 nm using a microtiter plate reader. Based on the inhibitor-concentration/response curves, IC_{50}-values were determined. For comparative purposes, IC_{50} values of the Laufer *et al.* reference (US 6,432,988) were determined as well. Further, the IC_{50} value of the known compound SB 203580 of the formula



was determined. Then, the ratio of the IC_{50} value of compound SB 203580 to the IC_{50} value of the tested compounds was calculated and presented in the attached table as SB/test. This ratio allows the direct comparability of all data. The higher the ratio, the more active is the tested compound.

As can be seen, the compounds of the present application are surprisingly more active as compared to the compounds of Laufer *et al.* and as compared to compound no. 24 which is compound 1 of Wagner *et al.* (J. Org. Chem. **2003**, 68, 4527-4530).

6. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

7. Further deponent saith not.

Ulm (Germany) Sep 14, 2007 W. Albrecht

[Ort], Germany, [Datum] (Wolfgang Albrecht)

Annex: Table 1

RELATED PROCEEDINGS APPENDIX

None.